Articles

Non-Insulin Dependent Diabetes Mellitus in Mexican-American Children

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To define the clinical and metabolic characteristics of children with non–insulin-dependent diabetes mellitus (NIDDM), we reviewed the medical records of 18 children and adolescents who met either or both of the following criteria for the diagnosis of the disease: evidence of continued endogenous secretion of insulin beyond that expected in insulin-dependent diabetes mellitus and satisfactory glycemic control with diet alone or in combination with an oral hypoglycemic agent more than 2 years from the time of diagnosis. Patients who met these criteria but had islet cell antibodies or insulin autoantibodies were eliminated from the study group. Patients with NIDDM constituted 8% of all patients with diabetes seen in our pediatric clinics and 19% of diabetic patients of Central or South American ancestry. Of the 18 patients, 12 (67%) were Mexican American. The mean age of onset was 12.8 years (range, 5 to 17). Obesity (n = 9) and acanthosis nigricans (n = 12) were common findings. Ketonuria was present at diagnosis in 5 (33%) of 15 patients and acidosis in 2 of 14 (14%). Challenge with a nutritional supplement (Sustacal, Mead Johnson Nutritionals) (n = 10) showed a mean fasting serum C-peptide concentration of 1.19 nmol per liter (3.6 ng per ml) and a mean concentration 90 minutes after stimulation of 2.96 nmol per liter (8.9 ng per ml). A family history of NIDDM was present in 13 (87%) of 15 patients, with 7 (47%) having 3 or more generations affected. Children with NIDDM are an important subset of those with diabetes, and this disease should be suspected in diabetic children presenting without ketoacidosis and with acanthosis nigricans, obesity, and a strong family history, particularly among those of Mexican-American ethnicity. Children with these characteristics should undergo testing of endogenous insulin secretion for appropriate therapeutic intervention.

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Diabetes mellitus has customarily been divided into the broad categories of type I or insulin-dependent diabetes (IDDM) and type II or non–insulin-dependent diabetes (NIDDM). Insulin-dependent diabetes is more common in childhood and is characterized by deficient endogenous insulin secretion with dependency on exogenous insulin for survival. Patients with NIDDM do not usually require insulin for survival, although insulin may be necessary for the optimal control of hyperglycemia.[1]

In the past, NIDDM had been considered a single disease that occurred almost exclusively in adults. Recent studies demonstrated a number of categories of diabetes mellitus that can be considered subclasses of NIDDM, some of which can occur in children and adolescents.[2–6]

To delineate the characteristics that distinguish children with NIDDM from those with IDDM, we reviewed the medical records of 18 patients with NIDDM being followed up in our pediatric diabetes clinics. We collected data regarding ethnic background, family history, physical and laboratory findings at diagnosis, measurements of endogenous insulin secretion, and treatment regimens.

Patients and Methods

We reviewed the medical records of all patients diagnosed with NIDDM at two southern California referral hospitals from July 1993 to January 1995 (13 patients). Five additional patients seen by us at other institutions were also included in the series. These five patients were not included in calculations of the prevalence of NIDDM in the clinic population. Patients were considered to have NIDDM if the following criteria were met:

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ABBREVIATIONS USED IN TEXT
IDDM = insulin-dependent diabetes mellitus
NIDDM = non–insulin-dependent diabetes mellitus

mal insulin secretion following the diagnosis of diabetes mellitus—as determined either by the measurement of C-peptide or insulin concentrations or by successful treatment with dietary management with or without oral hypoglycemic agents for more than two years after diagnosis, and 2) the absence of islet cell antibodies or insulin autoantibodies at the time of the diagnosis.

We recorded data regarding each patient's ethnic background, age at diagnosis, disease duration, and treatment regimen. A family history of diabetes mellitus was recorded according to the verbal report of the patients and their families. The presence or absence of the following at the time of diagnosis were recorded:

- Obesity, defined as a body mass index (weight in kilograms divided by the square of the height in meters) of greater than 27[7];
- Acanthosis nigricans, a dermatosis characterized by hyperpigmentation with velvety or verrucous hypertrophy of the skin, most prominent in flexural areas;
- Evidence of androgen excess in female patients, including hirsutism, menstrual irregularities and moderate to severe acne;
- Ketonuria at the presentation of diabetes; and
- Acidosis at presentation, defined as venous pH of less than 7.30 or a serum bicarbonate concentration of less than 20 mmol (mEq) per liter.

We also recorded the results of the evaluation of endogenous insulin secretion. The C-peptide response to a challenge with Sustacal (Mead Johnson Nutritionals, Princeton, NJ)—a nutritional supplement in beverage form that contains 33 grams of carbohydrate, 15 grams of protein, and 6 grams of fat per 8-oz serving—was assessed in 10 of the 18 patients. Children undergoing this protocol fasted overnight for a minimum of eight hours before the test. Patients treated with insulin omitted the morning insulin dose on the day of testing. Those receiving oral hypoglycemic agents discontinued these medications 48 hours before testing. Each subject ingested a standardized meal consisting of Sustacal in an amount corresponding to 30 kcal per kg of body weight for a maximum of 360 kcal. Blood specimens were obtained immediately before and 90 minutes after the ingestion of Sustacal for the measurement of serum glucose and C-peptide concentrations. Serum creatinine levels were measured in all patients to exclude the false elevation of C-peptide concentrations due to renal insufficiency.

Patients were diagnosed with NIDDM if the Sustacal challenge demonstrated serum C-peptide concentrations above those established by the Diabetes Control and Complications Trial as the upper limits of C-peptide secretion in IDDM: a fasting serum C-peptide concentration of greater than 0.2 nmol per liter (>0.6 ng per ml) and a 90-minute stimulated C-peptide concentration of greater than 0.5 nmol per liter (>1.5 ng per ml).[8]

Eight patients did not undergo a Sustacal challenge. For them, the following criteria were considered evidence of continued insulin secretion beyond that expected in IDDM:

- Random serum insulin concentration within or above the normal stimulated range of 215 to 1,075 pmol per liter (30 to 150 μU per ml).[9–11]
- Random serum C-peptide concentrations above 0.5 nmol per liter.[8]

No patient was being treated with insulin at the time of the measurement of serum insulin concentrations. Insulin and C-peptide concentrations were measured by radioimmunoassay, islet cell antibody levels were measured by indirect immunofluorescence, and islet autoantibody levels were measured by radioimmunoassay at a commercial laboratory (Nichols Institute, San Juan Capistrano, Calif). All tests for islet cell and insulin autoantibodies were done at the time of diagnosis, before therapy was started. All other laboratory studies were done in the chemistry laboratories of the participating institutions.

Differences in the prevalence of NIDDM among diabetic patients of different ethnicities were analyzed using the two-tailed Fisher exact test, with $P < 0.05$ considered significant.

Results

The case series comprised 18 patients with NIDDM (Table 1). Of these, 12 (67%) were Mexican American, 3 (17%) were white, 2 (11%) were African American, and 1 (5%) was Cambodian. Of the 18 patients, 13 were observed in our clinics, with the remaining 5 observed at neighboring institutions. Patients with NIDDM made up 3% of our non-Hispanic diabetic population (n = 107), 19% of our Hispanic diabetic population (n = 53), and 8% of our total group of patients with diabetes (n = 160). The odds ratio for the likelihood of NIDDM comparing Hispanic ethnicity to all other ethnicities was 8.06 (95% confidence interval, 1.92 to 47.10; $P < 0.001$).

The mean age at diagnosis of these diabetic patients was 12.8 years (range, 5 to 17). Obesity was present in 9 patients (50%) and acanthosis nigricans in 12 (67%). Of note, none of the 3 white patients had acanthosis nigricans. None of the female patients had signs or symptoms of hyperandrogenemia. Ketonuria was present at diagnosis in 5 (33%) of 15 patients tested and acidosis in 2 (14%) of 14.

Most of the patients had a family history of diabetes. Of 15 patients for whom the family history was known, 7 (47%) had family members in 3 or more generations diagnosed with diabetes. Six patients (40%) had only two generations known to be affected by diabetes. All

Table 1.—*Clinical Characteristics of Children with Non–Insulin-dependent Diabetes Mellitus**

Subject, no.	Gender	Ethnicity or Race	Age at Diagnosis, yr	BMI, kg/m²	Acanthosis Nigricans	Ketonuria	Acidosis	Duration of Disease, yr	Treatment
1....	Female	Mexican American	15	26.5	–	+	–	1.8	O
2....	Female	Mexican American	10	29.9	+	+	–	5.0	O
3....	Female	Mexican American	15	24.8	+	ND	–	2.0	O
4....	Female	Mexican American	13	30.9	+	–	–	0.8	I
5....	Male	Mexican American	14	33.6	+	–	–	2.2	O
6....	Male	Mexican American	14	32.2	+	+	+	0.8	O
7....	Female	Mexican American	10	23.0	–	–	–	4.3	O
8....	Male	Mexican American	5	17.2	+	+	ND	6.4	O
9....	Male	Mexican American	16	33.6	+	ND	–	1.8	D
10....	Female	Mexican American	17	19.2	+	–	ND	1.4	I†
11....	Female	Mexican American	12	25.2	+	ND	–	1.6	O
12....	Female	Mexican American + African American	15	33.9	+	–	–	0.1	D
13....	Male	White	16	29.2	–	–	ND	1.2	O
14....	Female	White	12	24.2	–	–	–	1.8	O
15....	Female	White	13	25.3	–	–	ND	4.3	O
16....	Female	African American	11	31.0	–	+	+	8.0	I + O
17....	Female	African American	12	24.0	+	–	–	2.3	D
18....	Male	Asian	10	28.7	+	–	–	4.2	I

D = diet, I = insulin, ND = not done, O = oral hypoglycemic agent

*The body mass index (BMI) was determined and the presence (+) or absence (–) of acanthosis nigricans, ketonuria, and acidosis assessed at the time of the initial diagnosis in all patients.
†Patient's diabetes was well controlled with a sulfonylurea agent until a regimen of prednisone was started after renal transplantation for chronic renal failure unrelated to her diabetes.

six had an affected parent. Two patients had no family members with known diabetes. Inheritance was maternal in 9 (69%) and paternal in 4 (31%) of the families. Overall, 13 (87%) of the 15 patients for whom the family history could be obtained had family histories of diabetes; 12 (80%) had an affected first-degree relative, and 11 (73%) had an affected parent.

Three patients (17%) in the study group are currently treated with insulin, with a mean daily dose of 1.2 units per kilogram. One patient is using a combination of insulin and an oral agent. Eleven patients (61%) are currently treated with oral hypoglycemic agents, and three (17%) are controlled with diet alone.

Sustacal challenge tests were performed in 10 of the 18 patients (Figure 1). Fasting serum C-peptide concentrations ranged from 0.33 to 2.45 nmol per liter (1.0 to 7.4 ng per ml), with a mean value of 1.19 nmol per liter (3.6 ng per ml). Stimulated serum C-peptide concentrations at 90 minutes ranged from 1.03 to 10.53 nmol per liter (3.1 to 31.8 ng per ml), with a mean value of 2.96 nmol per liter (8.9 ng per ml). Although there was variation among subjects, all had C-peptide concentrations greater than the values accepted by the Diabetes Control and Complications Trial as the upper limits of C-peptide secretion in IDDM.[8] One subject had chronic renal insufficiency, which likely contributed to the elevation in C-peptide concentrations (results from this patient were not included in the ranges or mean values listed above). For the eight patients who did not undergo Sustacal challenge tests, other criteria were used to establish the diagnosis of NIDDM. Six had clinical histories consistent with NIDDM according to the criteria previously stated. The remaining two patients had random and/or fasting serum insulin and C-peptide concentrations within or above the normal range.

Discussion

In this series, we describe the cases of 18 children and adolescents with NIDDM. Most (67%) were Mexican American, but white, African-American, and Asian children were also affected. The percentage of Mexican-American children in this series is higher than expected from census data that show 20% of the local population to be of Hispanic ethnicity.[12] Patients with NIDDM made up 8% of those with diabetes mellitus observed in our clinic and 19% of Hispanic patients with diabetes. In contrast, epidemiologic studies of children with IDDM have shown a lower-than-expected prevalence in Mexican Americans than in whites.[13] Because this study was retrospective and endogenous insulin secretion was not evaluated in all patients observed in the clinic, these figures may underestimate the prevalence of NIDDM among children with diabetes.

Of the 15 patients for whom the family history could be obtained, 13 (87%) had known family histories of

NIDDM, and 12 (80%) had an affected first-degree relative. Because NIDDM is frequently asymptomatic for prolonged periods and the age of onset varies, the prevalence of NIDDM among family members may be even higher than reported. Despite this bias, the observed percentages are higher than those in adults with NIDDM, 66% of whom have a family history of diabetes mellitus and 30% to 57% an affected first-degree relative.[14] Studies have shown, however, that there is an increased likelihood of a family history of diabetes in adult patients in whom diabetes mellitus develops at a younger age.[14] This finding is supported by the frequency of family histories of diabetes observed in this report. In contrast, studies of children with IDDM show that only 8% to 16% have a family history of IDDM and 1% to 24% have a family history of NIDDM.[13,15–17]

Obesity was present in half of our patients, similar to the 40% to 85% prevalence of obesity seen in adults with NIDDM.[18] In a recent study in a primarily African-American and white group, it was shown that an increase in the prevalence of NIDDM among children and adolescents correlated with an increase in the prevalence of obesity in the same population.[19]

Ketonuria and acidosis occurred in 6 (33%) and 2 (14%), respectively, of these patients at the time of diagnosis. In contrast, studies in patients with IDDM report ketonuria at presentation in 84% to 85% and acidosis in 48% to 62%.[15,20] Although ketonuria and acidosis are more frequently associated with IDDM, a number of studies have documented that they do occur under conditions of physiologic stress in adults with NIDDM.[2,21,22] One study in adults with NIDDM reported the presence of ketonuria in 34% and acidosis in 7% at diagnosis, similar to the frequency observed in this study.[22] Of our 18 patients with NIDDM, 4 (22%) currently require insulin to achieve glycemic control. This figure is comparable to the 17% to 37% of adults with NIDDM who require insulin.[21]

Studies of autoimmune markers in children with IDDM have shown that 84% have islet cell antibodies and 43% have insulin autoantibodies at the time of the diagnosis.[23,24] Because of the strong association of these autoimmune markers with IDDM in children, we chose to eliminate from our study any patient who tested positive for islet cell or insulin autoantibodies at diagnosis. It has been reported, however, that 3% to 27% of adults with NIDDM have islet cell antibodies.[25–27] The relevance of this finding in adults with NIDDM is still unclear, but it may represent an early stage of autoimmune IDDM.

Although additional physiologic studies are needed to evaluate the cause of impaired glucose tolerance in our patients, the increased serum insulin and C-peptide concentrations suggest that insulin resistance may be a component. The C-peptide concentrations during Sustacal challenge were within or above the range of normal, nondiabetic subjects,[9,28,29] with mean serum C-peptide concentrations comparable to those observed in studies of adults with NIDDM.[28–30] The variation in C-peptide responses to Sustacal observed among our patients has also been found in studies of adults with NIDDM.[30]

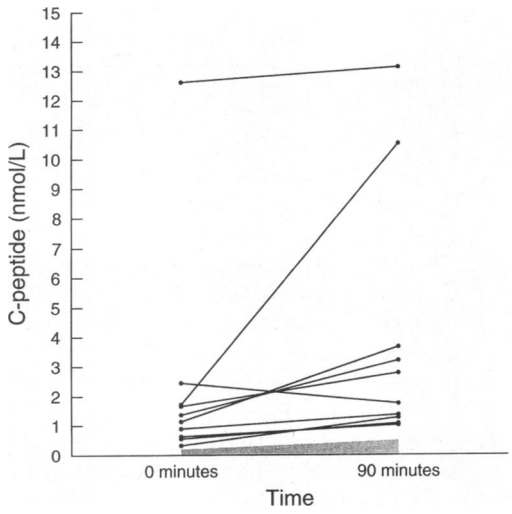

Figure 1.—The graph shows Sustacal challenge results (n=10). The shaded area represents limits of C-peptide secretion in IDDM as defined by the DCCT.[8] The patient had chronic renal insufficiency at the time of the test; C-peptide values may therefore be falsely elevated.

The group of children and adolescents with NIDDM described herein may represent not one disease but a final manifestation of a number of underlying disorders. Several subtypes of NIDDM have been reported in children, including maturity-onset diabetes of youth and various insulin-resistance syndromes. Maturity-onset diabetes of youth, as originally described by Fajans and co-workers, is characterized by an autosomal dominant inheritance pattern.[3,31] Affected persons have mild, slowly progressive diabetes that can be controlled for prolonged periods with diet alone or in combination with oral hypoglycemic agents. Obesity and acanthosis nigricans are not frequently associated features.[3,4,31] Genetic studies linked maturity-onset diabetes of youth to defects in the glucokinase gene and the genes for hepatocyte nuclear factor-1α and -4α.[31–36] Glucokinase mutations are thought to affect the glucose-sensing mechanism of the β-cells, raising the threshold for insulin secretion. A variant of maturity-onset diabetes of youth has also been described in African-American patients.[34] These patients have no evidence of autoimmunity, but have severely impaired β-cell function. Insulin secretion is below that observed in normal control subjects but above that of patients with IDDM. Although these patients typically require insulin, they are not insulin-dependent as they are able to discontinue its use for prolonged periods without the development of ketoacidosis.[34]

Acanthosis nigricans is thought to be a cutaneous marker for insulin resistance[37] and was the most frequent physical finding in our study, present in two thirds of the patients. Of note, acanthosis nigricans was not

present in any of the three white patients. This dermatosis is a component of a number of diabetic syndromes, but it can also occur in obese persons with or without diabetes.[6,37–41] Of the insulin resistance syndromes, the "HAIR-AN" syndrome is probably the most common. This disorder occurs in adolescent and adult women and is characterized by hyperinsulinemia, impaired glucose tolerance, acanthosis nigricans and hyperandrogenism.[6,39] Although most of our patients with acanthosis nigricans had increased serum C-peptide concentrations consistent with insulin resistance, none had the hyperandrogenic features characteristic of the "HAIR-AN" syndrome.

Most of the patients in this series are Mexican American, an ethnic group in which adults have a high prevalence of NIDDM relative to non-Hispanic whites.[18,42] Mexican-American adults with NIDDM also frequently have strong family histories of diabetes, similar to the patients reported here.[43] Some authors hypothesize that the high prevalence of NIDDM in Mexicans is related to their shared gene pool with Native Americans, a group with a high prevalence of NIDDM.[44,45]

Herein, we describe 18 patients, ages 5 to 17, with NIDDM. These patients were predominantly Mexican American, with a high prevalence of obesity and acanthosis nigricans and strong family histories of NIDDM. Our data suggest that NIDDM may be more common in Mexican-American children than perviously suspected. An increased awareness of NIDDM among physicians is needed to accurately diagnose and appropriately treat these patients.

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